Docket No.: 025444.1132-US01
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Melton B. Affrime, *et al.*

Application No.: 09/760,588 Art Unit: 1614

Filed: January 16, 2001 Examiner: C. Delacroix-Muirheid

For: TREATING ALLERGIC AND
INFLAMMATORY CONDITIONS

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under 37 C.F.R. §§ 41.37(a) and (e), this brief is filed within six months of the Notice of Appeal filed in this case on November 17, 2005, and is in furtherance of said Notice of Appeal.

The fees required under 37 C.F.R §§ 41.20(b)(2) and 1.17(a) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF. It is not believed that additional fees or extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional fees or extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including additional fees required for this appeal) are hereby authorized to be charged to our Deposit Account No. 50-0740.

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This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and Manual of Patent Examining Procedure § 1206:

I. Real Party In Interest
II Related Appeals, Interferences, and Judicial Proceedings
III. Status of Claims
IV. Status of Amendments
V. Summary of Claimed Subject Matter
VI. Grounds of Rejection to be Reviewed on Appeal
VII. Argument
VIII. Claims
IX. Evidence
X. Related Proceedings
XI. Conclusion
Appendix A: Claims Appendix
Appendix B: Evidence Appendix (U.S. Patent Appln. Pub. No. US 2003/0004179)
Appendix C: Related Proceedings Appendix

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is:

Schering Corporation (assignee of the present application).

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

There are no other prior or pending appeals, interferences, or judicial proceedings that may be related to, will directly affect or will be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are sixteen (16) claims pending in the above-captioned application. Claims 69, 73, 76, 79, 80 and 81 are the independent claims.

B. Current Status of Claims

1. Claims cancelled: 1-68

2. Claims withdrawn from consideration but not cancelled: None

3. Claims objected to: None

4. Claims pending: 69-84

5. Claims allowed: None

6. Claims rejected: 69-84

C. Claims on Appeal

The claims on appeal are claims 69-84.

IV. STATUS OF AMENDMENTS

The Final Rejection was mailed on June 16, 2005. Applicants did not file an Amendment After Final Rejection. On September 16, 2005, Applicants filed a Response After Final Action that did not propose any amendments to any of the claims. Therefore, the claims at issue are those that were presented in the Amendment in Response to Non-Final Office Action, dated March 28, 2005. On October 19, 2005, an Advisory Action Before Mailing of Appeal Brief (hereinafter the "Advisory Action") was mailed. That Advisory Action stated that, for purposes of appeal, the proposed response would be entered to remove the rejection under 35 U.S.C. § 112 ¶ 2 (*see* Section VI, below). A Notice of Appeal and a Request for Oral Hearing were filed on November 17, 2005.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention pertains to the administration of desloratadine, a non-sedating antihistamine approved by the Food and Drug Administration.[1] *See, e.g.,*

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[1] The full chemical name of desloratadine is 8-chloro-6-11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cycloheptic[1,2-b]pyridine. The compound is also known as "DCL" and "descarbonylethoxyloratadine."

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, enter "desloratadine". Specifically, the present invention provides for oral administration of desloratadine to produce a target steady state serum or pharmacokinetic profile of desloratadine that is therapeutically effective without toxicity. That target steady state pharmacokinetic profile of desloratadine comprises an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose. Appl. No. 09/760,588 (hereinafter "the '588 application" or "the present application"), page 21, lines 8-15. This may be achieved, for example, by daily administration of 5 mg of desloratadine for seven days or more. *Id.* at page 18, lines 20-24.

Independent claim 69 is directed to a method of administering a pharmaceutical composition (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) to target a steady state pharmacokinetic profile of desloratadine comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

Independent claims 73 and 76 are directed to administering a pharmaceutical composition (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) once a day for about 10 days (claim 73), or for a period of time (claim 76), to target the steady state desloratadine pharmacokinetic profile identified above.

Independent claim 79 is directed to a method for achieving a pharmacokinetic profile of desloratadine that is safe and effective for treating nasal and non-nasal

symptoms of seasonal and perennial allergic rhinitis and for treating symptoms of chronic idiopathic urticaria in a human 12 years or older. This method is carried out by administering a dosage form (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) to target a steady-state pharmacokinetic profile of desloratadine comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

Independent claims 80 and 81 are directed, respectively, to a method of treating nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis in a human 12 years or older, and a method of treating symptoms of chronic idiopathic urticaria in a human 12 years or older. In both claims, this method is safe and effective for treating the relevant symptoms, and is carried out by administering a dosage form (comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent) to target the steady state pharmacokinetic profile identified above.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

In the June 16, 2005 Final Rejection, claims 69-84 were rejected under 35 U.S.C. § 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. In the October 19, 2005 Advisory Action, that rejection was determined to have been overcome by Applicants' September 16, 2005 Response After Final Action.

In addition, claims 69-84 were also finally rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,100,274 ("the Kou patent" (commonly owned

with the '588 application by Schering Corporation)). In the October 19, 2005 Advisory Action, that rejection was determined not to have been overcome by Applicants' September 16, 2005 Response After Final Action. Accordingly, the rejection under 35 U.S.C. § 102(e) is the ground of rejection to be reviewed on appeal.

VII. ARGUMENT

Independent claims 69, 73, 76, 79, 80 and 81 (and dependent claims 70-72, 74-75, 77-78 and 82-84) stand rejected under 35 U.S.C § 102(e) as anticipated by the Kou patent. In the Final Rejection, the Examiner argues that the Kou patent "discloses administration of a pharmaceutical composition containing an identical compound, i.e., desloratadine, at identical dosages, i.e., 5 mg/day, using applicant's claimed method steps." The Examiner concludes that "treatment of nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis as well as chronic idiopathic urticaria . . . would be inherent" and that "one of ordinary skill in the art is able readily to envisage about 10 days of treatment" from the disclosure of the Kou patent.

The Kou patent teaches stable pharmaceutical compositions comprising desloratadine, a desloratadine-protective amount of a pharmaceutically acceptable basic salt such as calcium dibasic phosphate, and an amount of at least one disintegrant. Column 5, lines 44-54 of the Kou patent states that "the anti-allergic effective amount of [desloratadine] for oral administration" is preferably about 5 to 10 mg/day in single or divided doses, and most preferably 5 mg, once a day. Column 5, lines 49-56 specifically states:

> Of course the precise dosage and dosage regimen may be varied depending upon the requirements of the patients (e.g., his or her sex, age) as well as the severity of the allergic condition being treated.

> Determination of the proper dosage and dosage regimen for a particular patient will be within the skill of the attending clinician.
>
> Descarbonylethoxyloratadine possess *[sic]* antihistaminic properties.

A.

In the Advisory Action, the Examiner reiterates that "[i]t is reasonable to conclude that the same patient is being administered the same composition by the same mode of administration in the same amount in both the instant claims and the Kou reference." Citing *In re Woodruff*, 16 USPQ 2d 1934, 1936 (Fed. Cir. 1990), the Examiner continues, "[t]he fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on the method."

The Advisory Action does not contend, however, that the Kou patent discloses how to achieve a steady state pharmacokinetic profile of desloratadine, including, for example, the time period for daily administration of desloratadine to achieve a steady state pharmacokinetic profile. Indeed, the Advisory Action does not contend that the Kou patent discloses any particular steady state pharmacokinetic profile of desloratadine, let alone a steady state pharmacokinetic profile that should be targeted.

The Examiner's reliance on *In re Woodruff, supra,* is misplaced on the law and the facts. First, the rejections upheld in *Woodruff* were under 35 U.S.C. § 103, not, as here, under 35 U.S.C. § 102. Second, contrary to the statement in the Advisory Action, Applicants have not "merely" discovered yet another beneficial effect from the method set forth in the prior art. Rather, they have invented a new method -- that is, administering desloratadine to achieve a specified steady state pharmacokinetic profile of

desloratadine that has been found to be safe and effective. This is not explicitly disclosed by the Kou patent, nor is it inherent in that disclosure.

B.

In the Final Rejection, the Examiner states:

> The claims are anticipated by Kou because Kou discloses administration of a pharmaceutical composition containing an identical compound, i.e., desloratadine, at identical dosages, i.e., 5 mg/day, using applicant's claimed method steps. Accordingly, treatment of nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis as well as chronic idiopathic urticaria in a human 12 years or older *would be inherent.* (emphasis added)

This statement, however, omits to mention that each of the pending claims in the present application also specifies a steady state pharmacokinetic profile to be targeted by the administration of desloratadine. The Examiner has not and, we believe, cannot explain how the Kou patent discloses, explicitly or inherently, the steady state desloratadine pharmacokinetic profile specified in the claims of the present application.

C.

The Examiner has applied the incorrect standard for inherent anticipation. As the Federal Circuit confirmed in *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991), "[i]nherency … may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not the test." The proper test for inherent anticipation is whether the claimed invention "necessarily results from" the disclosure in the allegedly inherently anticipating reference. (*See, e.g., Nicholas v. Perricone, M.D. v. Medicis Pharmaceutical Corporation,* 432 F.3d 1368, 1377-1380 (Fed. Cir. 2005); *Schering Corp. v. Geneva Pharmaceutials, Inc.,* 339 F.3d 1373, 1381 (Fed. Cir. 2003); and *Rapoport v. Dement,* 254 F.3d 1053, 1062-63 (Fed. Cir. 2001).) These Federal Circuit requirements are

reflected in the Manual of Patent Examining Procedure (hereinafter "MPEP"). Specifically, MPEP Section 2112, part IV states, "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112, part IV (Rev. 3, August 2005) at at 2100-57 (emphasis in original).

The Examiner does not explain how practicing the disclosure of the Kou reference would necessarily result in the steady state desloratadine pharmacokinetic profile specified in each of the pending claims of the present application. Instead, the Examiner argues that "one of ordinary skill in the art is able to *readily envisage* about 10 days of treatment from the disclosure of Kou and is therefore anticipated." (Emphasis added)

A conclusion of inherent anticipation, however, requires more than an argument that a person of ordinary skill is able to "readily envisage" the claimed invention, as suggested by the Final Rejection. As made clear by the Federal Circuit cases and MPEP provisions cited above, to sustain a conclusion of inherency, an Examiner must find that the extrinsic evidence makes clear that a person of ordinary skill would recognize that "the missing descriptive matter is *necessarily present* in the thing described in the reference." MPEP, § 2112, part IV, at 2100-57 (emphasis added). In other words, the Examiner has not argued that the disclosure of the Kou patent meets the standard required to conclude that it inherently anticipates Applicants' claimed invention.

D.

The Final Rejection and the Advisory Action are deficient in another important respect. The MPEP expressly requires the Examiner to provide "rationale or evidence tending to show inherency." MPEP, § 2112, part IV, at 2100-57. Specifially, the MPEP

states, "'In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)(emphasis in original)." MPEP, *supra* at 2100-57.

In *Ex parte Levy,* the Examiner did not provide objective evidence or cogent technical reasoning to support a conclusion of inherency, and the Board reversed. The same result should obtain here. The Examiner has not provided any objective evidence to support the conclusion of inherency. Nor has the Examiner provided a cogent technical explanation for that conclusion. To the contrary, the Examiner has not provided anything to rebut Applicants' showing that the specified steady state desloratadine pharmacokinetic profile does not, in fact, necessarily result from the disclosure of the Kou patent.

In particular, the Examiner did not address Applicants' argument, in their Response After Final Rejection, that the Kou patent does not discuss how to administer desloratadine in order to achieve an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL. Nor did the Examiner address Applicants' argument that the Kou patent does not discuss how to achieve an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose. Response After Final Rejection, page 5, line 21 - page 6, line 8.

The Kou patent does not teach a duration of administration, and therefore encompasses administration of 5 mg of desloratadine for a single day, or daily

administration of 5 mg of desloratadine for any number of days, including periods of less than about seven days. The present application -- not the Kou patent -- teaches that these periods of administration would not necessarily establish the steady state pharmacokinetic profile of the claimed invention. Yet the Examiner also did not respond to Applicants' observations that the Kou patent does not disclose or suggest either the pharmacokinetic profile that would result from administering a single desloratadine tablet, or the number of days for which administration of desloratadine is necessary to achieve a steady state phamacokinetic profile, as specifically contemplated in the claims of the present application. The Examiner also has not explained how the claimed steady state pharmacokinetic profile necessarily results from the express teaching of the Kou patent that the precise dosage and dosage regimen can be modified depending on the requirements of the patients as well as the severity of the allergic condition being treated. Kou patent, col. 5, lines 49-52.

E.

Beyond failing to provide objective evidence or cogent technical explanation required to sustain an inherency argument, the Examiner has also not addressed Appliants' additional evidence confirming that the Kou patent does not necessarily or inherently disclose the steady state pharmacokinetic profile of the claimed invention. In their Response to Final Action (37 C.F.R. Section 1.116), filed on September 16, 2005, Applicants cited U.S. Patent Appln. Pub. No. US 2003/0004179 (hereinafter "the Affrime application") for the proposition that the pharmacokinetic profile of desloratadine is

variable and can be affected by factors not disclosed in the Kou patent.[2] For example, the Affrime application reports on the results of a clinical trial involving administration of a 5 mg desloratadine tablet to certain adult patients under fasting conditions. Affrime application, ¶¶ 0028 - 0060. The Kou patent, in contrast, does not disclose whether the disclosed 5 mg desloratadine tablet was or is to be administered to patients under fasting conditions, or before or after eating and does not report any phramacokinetic data. The Affrime application reports that, under fasting conditions, the administration of a 5 mg tablet of desloratadine resulted in a pharmacokinetic profile with a mean C_{max} of 2.19 ng/mL. Affrime application, Tables 1 and 2 at p. 4. This C_{max} value is only slightly more than half of the arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) value of about 4 ng/mL claimed by Applicants in the present application. This suggests that at least one factor not disclosed in the Kou patent may affect the pharmacokinetic profile of people administered 5 mg of desloratadine daily. Therefore, this provides further confirmation that the teaching of the Kou patent does not necessarily result in the target steady state pharmacokinetic profile of the claimed invention.

For this reason, this case should be guided by the Federal Circuit's decision in *Toro Co. v. John Deere & Co.*, 355 F.3d (Fed. Cir. 2004). In *Toro*, the Federal Circuit affirmed a District Court finding that the claimed invention was not inherently disclosed by the cited prior art reference. The District Court had found that "no reasonable

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[2] A copy of the Affrime application is attached at Appendix B. The Affrime application, the Kou patent, and the present application are commonly owned by Schering Corporation.

factfinder could find that one of skill in the art would discern from the [prior art reference] the unique combination of factors" that would necessarily result in the claimed invention." *Id.* at 1319. Likewise in this case, as the Affrime application suggests, there is at least one factor -- namely, the fasting or eating state of the subject -- that cannot be discerned from the Kou reference, that may affect the subject's pharmacokinetic profile, and that may therefore affect whether the teaching of the Kou reference will necessarily result in the claimed invention. This provides another basis for reversing the Examiner's finding of inherency.

F.

In sum, the Examiner has not provided the required objective evidence or cogent technical explanation of how or why Applicants' claimed invention necessarily results from the teachings of the Kou patent. Nor has the Examiner addressed Applicants' showing that their claimed invention would not, in fact, necessarily result from the Kou patent. The Examiner's finding of inherency therefore should be reversed.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached as Appendix A.

IX. EVIDENCE

As noted above, attached hereto as Appendix B is a copy of U.S. Patent Appln. Pub. No. US 2003/0004179. This document was cited in Applicants' Response After Final Rejection (37 C.F.R. Section 1.116), filed on September 16, 2005, which was entered into the record by the Examiner in the Advisory Action dated October 19, 2005.

X. RELATED PROCEEDINGS

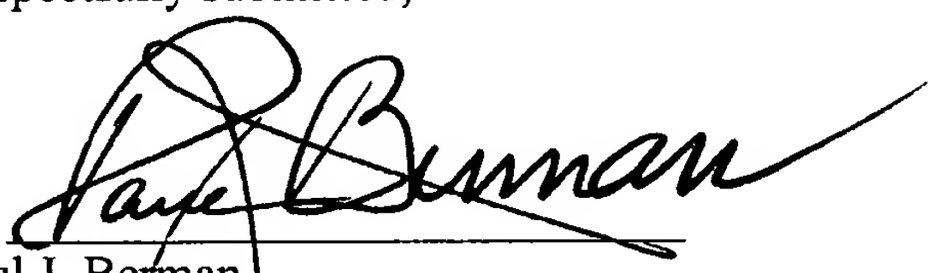
Attached hereto in Appendix C is a statement confirming that there are no other prior or pending appeals, interferences, or judicial proceedings that may be related to, will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

XI. CONCLUSION

Applicants respectfully urge that the rejection of claims 69-84 as being unpatentable under 35 U.S.C. § 102(e) is improper, and that this rejection be reversed.

Dated: April 19, 2006

Respectfully submitted,



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APPENDIX A

CLAIMS

Claims 1-68 (Cancelled).

69. A method of administering a pharmaceutical composition, wherein the method comprises:

administering the pharmaceutical composition, comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, to target a pharmacokinetic (pK) profile for desloratadine comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

70. The method of claim 69, wherein the pharmaceutical composition comprises about 5.0 mg of desloratadine.

71. The method of claim 70, wherein the pharmaceutical composition is administered once a day.

72. The method of claim 69, wherein the desloratadine is in a free base form.

73. A method of administering a pharmaceutical composition, comprising:

administering the pharmaceutical composition, comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, once a day for about 10 days, wherein said administering is carried out to target a pharmacokinetic (pK) profile comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

74. The method of claim 73, wherein the pharmaceutical composition comprises about 5.0 mg of desloratadine.

75. The method of claim 73, wherein the desloratadine is in a free base form.

76. A method of administering a pharmaceutical composition comprising:

administering the pharmaceutical composition, comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, for a period of time to target the establishment of a steady-state pharmacokinetic (pK) profile in the bloodstream of a patient comprising an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

77. The method of claim 76, wherein the pharmaceutical composition comprises about 5.0 mg of desloratadine.

78. The method of claim 76, wherein the desloratadine is in a free base form.

79. A method of achieving a pharmacokinetic (pK) profile of desloratadine that is safe and effective for treating nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis and for treating symptoms of chronic idiopathic urticaria in a human 12 years or older, comprising:

administering a dosage form comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, wherein said administering is carried out to target the pK profile and wherein the pK profile comprises an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

80. A method of treating nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis in a human of 12 years and older comprising:

administering a dosage form comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, wherein said administering is carried out to target a pharmacokinetic (pK) profile that is safe and effective for treating the allergic rhinitis symptoms, and wherein the pK profile comprises an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

81. A method of treating symptoms of chronic idiopathic urticaria in a human of 12 years and older comprising:

administering a dosage form comprising desloratadine and a suitable, inert pharmaceutically acceptable carrier or diluent, wherein said administering is carried out to target a pharmacokinetic (pK) profile that is safe and effective for treating the chronic idiopathic urticaria symptoms, and wherein the pK profile comprises an arithmetic or geometric mean steady state maximum plasma concentration (C_{max}) of desloratadine of about 4 ng/mL, and an arithmetic or geometric mean time to maximum plasma concentration (T_{max}) of desloratadine of about 3 hours post dose.

82. The method of any of claims 79, 80 or 81, wherein said administering is carried out according to a dosage regimen comprising administering the dosage form once a day for about 10 days.

83. The method of any of claims 79, 80 or 81, wherein said dosage form comprises about 5.0 mg of desloratadine.

84. The method of any of claims 79, 80 or 81, wherein the desloratadine is in a free base for

APPENDIX C

There are no other prior or pending appeals, interferences, or judicial proceedings that may be related to, will directly affect or will be directly affected by or have a bearing on the Board's decision in this appeal.